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The Journal of
THORACIC AND CARDIOVASCULAR SURGERY

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CARDIOPULMONARY SUPPORT AND PHYSIOLOGY

NEUROPSYCHOLOGIC OUTCOME AFTER DEEP HYPOTHERMIC CIRCULATORY ARREST IN ADULTS

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Introduction: **Pediatric patients undergoing prolonged periods of deep hypothermic circulatory arrest have been found to experience long-term deficits in cognitive function. However, there is limited information of this type in adult patients who are undergoing deep hypothermic circulatory arrest for thoracic aortic repairs.** *Methods:* **One hundred forty-nine patients undergoing elective cardiac or thoracic aortic operations were evaluated preoperatively; 106 patients were evaluated early in the postoperative period (EARLY), and 77 patients were evaluated late in the postoperative period (LATE) with a battery of neuropsychologic tests. Seventy-three patients had routine cardiac operations without deep hypothermic circulatory arrest, and 76 patients with deep hypothermic circulatory arrest were divided into 2 subgroups: those with 1 to 24 minutes of deep hypothermic circulatory arrest (n = 36 patients) and those with 25 minutes or more of deep hypothermic circulatory arrest (n = 40 patients). The neuropsychologic test battery consisted of 8 tests encompassing 5 domains: attention, processing speed, memory, executive function, and fine motor function. Data were normalized to baseline values, and changes from baseline were analyzed by analysis of covariance, multivariate logistic regression, and survival functions.** *Results:* **In all domains, poor performance or inability to be tested EARLY were significant predictors of poor performance LATE (odds ratio, 5.27; $P < .01$). Deep hypothermic circulatory arrest of 25 minutes or more and advanced age were significant predictors of poor performance LATE for the memory and fine motor domains. Deep hypothermic circulatory arrest of 25 minutes or more (odds ratio, 4.0; $P = .02$) was a determinant of prolonged hospital stay (>21 days).** *Conclusion:* **Deep hypothermic circulatory arrest of 25 minutes or more and advanced age were associated with memory and fine motor deficits and with prolonged hospital stay. (J Thorac Cardiovasc Surg 1999; 117:156-63)**

There is compelling evidence in pediatric patients that prolonged periods of deep hypothermic circulatory arrest (DHCA) are associated with long-term deficits in cognitive function.[1-5] Although DHCA is widely used in operations of the thoracic aorta in adults, there is only one retrospective cognitive outcome study.[6] The evaluation of neurologic outcome in adult patients undergoing DHCA has otherwise been limited to reports of the incidence of postoperative stroke and gross neurologic dysfunction.[7,8] The incidence of and factors associated with

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long-term neuropsychologic dysfunction are largely unknown. The current study was undertaken to examine this question in patients undergoing cardiac operations with and without periods of DHCA.

Patients and methods

In compliance with an Institutional Review Board–approved protocol concerning informed patient consent, patients undergoing elective cardiac or thoracic aortic operations were evaluated with a battery of neuropsychologic tests at up to 3 intervals. For a baseline measurement, 149 patients were tested preoperatively (PRE). After the operation, 106 patients were tested as early in the postoperative period (during the same hospitalization) as was compatible with their medical condition (EARLY). Finally, 77 patients were tested after hospital discharge at the outpatient follow-up visit (LATE). The length of stay in the hospital and any reasons that neuropsychologic testing could not be completed were recorded for each patient.

Of the 149 patients, 73 patients had a routine cardiac operation without DHCA, and 76 patients had a thoracic aortic operation with varying periods of DHCA. Patients receiving DHCA were subdivided into 2 groups, those with 1 to 24 minutes of DHCA ($n = 36$) and those with 25 minutes or more of DHCA ($n = 40$). This cutoff value was chosen for the following reasons: (1) It represents the median DHCA time in this cohort of patients; (2) it divides more simple Bentall procedures from complex aortic arch repairs; and (3) on review of the pilot data, it represented the point above which neuropsychologic deficits became more prevalent.

The surgical technique for induction of profound hypothermia and use of circulatory arrest were constant throughout the duration of the study and have been described in detail previously.[7] Briefly, central cooling on cardiopulmonary bypass (CPB) was performed with alpha-stat blood gas management to produce profound total body hypothermia to a core temperature of 12°C to 15°C, as measured in the esophagus. A minimum duration of 30 minutes is usually required for cooling thoroughly enough to prevent upward drift of body temperature during prolonged DHCA. We used jugular bulb saturation as an indicator of cerebral cooling and concomitant cerebral metabolic suppression. Jugular bulb oxyhemoglobin saturation was monitored every 5 minutes during the cooling phase before DHCA, and cooling was continued until the jugular venous saturation exceeded 95% in most cases and 90% in all. During DHCA, the head was packed in ice to prevent warming of the central nervous system.

On completion of the procedure, gradual warming was carried out by means of CPB, limiting the gradient between blood and body temperature to less than 10°C, with a maximum blood temperature of 37°C. A warming blanket was also used. Central warming was usually discontinued at an esophageal temperature of 35°C to 37°C and a rectal or bladder temperature of 30°C to 35°C.

In control patients, whose operations were performed with CPB alone, the operations were carried out under mildly hypothermic conditions, with an average temperature during aortic crossclamping of 28°C to 30°C. The duration of CPB in these patients was 125 ± 51 minutes.

All patients undergoing DHCA were given 30 mg · kg^{-1} of methylprednisolone before DHCA. Glucocorticoids were continued in tapering doses for 48 hours in patients with an interval of DHCA exceeding 30 minutes.

Neuropsychologic evaluation. The neuropsychologic battery consisted of 8 tests with the data consolidated into 5 domains.

1. Attention: WAIS-R Digit Span subtest (Wechsler Adult Intelligence Scale–Revised; Psychological Corporation, New York, NY).
2. Processing speed: The Trail Making Test, Part A (Halstead-Reitan Neuropsychological Test Battery; Neuropsychology Press, Tucson, Ariz), and the Symbol Digit Modalities Test, oral version (Western Psychological Services, Los Angeles, Calif).
3. Memory: The Logical Memory subtest (Wechsler Memory Scale—Revised; The Psychological Corporation, San Antonio, Tex) and the Verbal Paired Associates subtest (Wechsler Memory Scale—Revised; The Psychological Corporation). Three different forms of these tests were administered at the 3 evaluation times, and the test form presentation was randomly ordered across the 3 evaluation times: For logical memory, the first Wechsler Memory Scale–Revised Logical Memory story, the second Wechsler Memory Scale–Revised Logical Memory story, and one story from the Wechsler Memory Scale were used.[9] For verbal paired associates, word pairs from the Wechsler Memory Scale–Revised, the Wechsler Memory Scale, and one set created by the Mt Sinai Department of Rehabilitation Medicine were used.
4. Executive function: The Trail Making Test, Part B (The Halstead-Reitan Neuropsychological Test Battery; Neuropsychology Press) and the Similarities subtest (Wechsler Adult Intelligence Scale—Revised; Psychological Corporation).
5. Fine motor function: The Finger Tapping Test (Psychological Assessment Resources, Inc, Odessa, Fla) and the Grooved Pegboard Test (Psychological Assessment Resources, Inc). The dominant hand was tested.

Data analysis. The initial step in this analysis was consolidating the data from 8 neuropsychologic tests into composite scores for each cognitive domain. Composite scores were computed by standardizing each neuropsychologic measure with the mean and standard deviation of the entire patient sample at baseline (PRE). For each patient, the standardized score (Z-score) was calculated for each test by subtracting the mean of all subjects' test scores at baseline from the individual test score and by dividing this difference by the standard deviation for all subjects at baseline. The composite score was defined as the average Z-score for all tests (for which data were available) within each cognitive domain at each testing interval. For example, a patient Z-score of +1.0 repre-

Table I. *Mean and standard deviation of Z-scores for all domains at each evaluation time and the change in mean Z-score at EARLY and LATE neuropsychologic testing after the operation*

	Before the operation	*EARLY after the operation*	*LATE after the operation*	*Difference: before the operation–EARLY after the operation*	*Difference: before the operation–LATE after the operation*
Attention					
No DHCA	−0.03 ± 1.11	−0.21 ± 1.22	−0.11 ± 0.92	−0.18	−0.08
DHCA: 1-24 min	0.19 ± 0.83	0.03 ± 0.91	0.48 ± 0.78	−0.16	+0.29
DHCA: ≥25 min	−0.10 ± 0.92	−0.54 ± 0.99	0.16 ± 0.80	−0.44	+0.26
Processing speed					
No DHCA	−0.10 ± 0.74	−0.21 ± 0.82	−0.10 ± 0.83	−0.11	0.00
DHCA: 1-24 min	0.20 ± 0.92	0.48 ± 3.48	0.44 ± 0.63	+0.28	+0.24
DHCA: ≥25 min	0.00 ± 1.46	0.60 ± 3.31	0.03 ± 0.57	+0.60	+0.03
Memory					
No DHCA	−0.03 ± 1.05	−0.26 ± 1.15	0.36 ± 0.89	−0.23	+0.39
DHCA: 1-24 min	0.17 ± 0.88	0.03 ± 1.22	0.62 ± 1.00	−0.14	+0.45
DHCA: ≥25 min	−0.11 ± 1.02	−0.59 ± 0.96	−0.39 ± 0.83	−0.48	−0.28
Executive					
No DHCA	−0.05 ± 0.92	−0.04 ± 0.95	−0.01 ± 0.79	+0.01	+0.04
DHCA: 1-24 min	0.13 ± 0.83	0.30 ± 0.91	0.09 ± 0.44	+0.17	−0.04
DHCA: ≥25 min	−0.03 ± 1.28	0.72 ± 1.36	0.25 ± 0.88	+0.75	+0.28
Fine motor					
No DHCA	−0.01 ± 0.91	−0.10 ± 1.05	0.39 ± 1.02	−0.09	+0.40
DHCA: 1-24 min	0.31 ± 1.14	0.14 ± 1.17	0.76 ± 1.00	−0.17	+0.45
DHCA: ≥25 min	−0.26 ± 1.01	−0.81 ± 1.08	−0.36 ± 0.69	−0.55	−0.10

sents a result that was 1 standard deviation above average, compared with all patients before the operation. If the other variable in that domain yielded a Z-score of −0.2, then the domain composite score was +0.4 for that patient at that time interval. Analysis of covariance was performed on the change in composite Z-score data from baseline, with age, duration of DHCA, and interval between the operation and testing date as the covariates.

For each individual and each cognitive domain, data for the EARLY and LATE postoperative tests were dichotomized to reflect either negative or positive neuropsychologic outcome, relative to the baseline examination. For the EARLY test, negative neuropsychologic outcome was defined as a decrease in Z-score greater than 1.0 or an inability to be tested because of illness. For the LATE test, negative neuropsychologic outcome was defined as any decline in Z-score to account for improvement because of practice effects and recovery from the operation. These cutoff values were chosen prospectively.

A multivariate logistic regression analysis was performed to determine the relative influence of patient age and duration of hypothermic circulatory arrest for each domain. Additionally, the predictive ability of negative EARLY neuropsychologic outcome was introduced into the multivariate model. The data are presented as odds ratios and 95% confidence limits. Survival functions were performed to analyze the influence of exposure to DHCA and age on hospital length of stay.

Results

One hundred forty-nine patients underwent neuropsychologic evaluations before the operation, and these data were used to establish baseline normative data. One hundred six patients underwent neuropsychologic evaluations during the EARLY testing interval. This testing occurred between 3 and 35 days after the operation (median, 7 days). Patients whose first postoperative evaluations were later tended to be more ill, often requiring longer periods of mechanical ventilation. Several patients were too ill to be tested at all (n = 16 patients). Seventy-seven patients underwent neuropsychologic evaluations during the LATE testing interval at the outpatient postoperative follow-up visit. This testing occurred between 16 and 129 days after the operation (median, 54 days). The number of days between the EARLY and LATE testing intervals ranged from 9 to 123 (median, 45 days).

The 73 patients with no DHCA were aged 64 ± 13 years (37% women). Two of these patients had strokes; one was able to undergo EARLY and LATE testing, and the other was lost to follow-up. None of the patients in the group with no DHCA died during hospitalization. The 36 patients with 1 to 24 minutes of DHCA were aged 55 ± 16 years (14% women); there were no strokes or deaths in this group. The 40 patients

Table II. *Analysis of covariance for different durations of DHCA and age*

	EARLY results	*LATE results*
Attention		
DHCA: 0 vs 1-24 min	−0.11 (−0.74, 0.52)	0.14 (−0.43, 0.71)
DHCA: 0 vs ≥25 min	−0.42 (−1.07, 0.23)	−0.08 (−0.67, 0.51)
Age	−0.006 (−0.016, 0.004)	−0.007 (−0.021, 0.007)
Processing speed		
DHCA: 0 vs 1-24 min	0.61 (−0.84, 0.06)	0.15 (−0.50, 0.80)
DHCA: 0 vs ≥25 min	0.59 (−0.98, 2.16)	0.03 (−0.66, 0.72)
Age	0.004 (−0.016, 0.024)	−.005 (−0.019, 0.009)
Memory		
DHCA: 0 vs 1-24 min	0.07 (−0.54, 0.68)	0.18 (−0.37, 0.35)
DHCA: 0 vs ≥25 min	−0.45 (−1.10, 0.20)	−0.75 (−1.34, −0.16)
Age	−0.024 (−0.034, −0.014)	−0.018 (−0.030, −0.006)
Executive		
DHCA: 0 vs 1-24 min	2.23 (−1.04, 5.50)	1.54 (−1.91, 4.99)
DHCA: 0 vs ≥25 min	1.34 (−2.16, 4.86)	0.35 (−3.39, 4.09)
Age	−0.10 (−0.16, −0.04)	−0.15 (−0.23, −0.07)
Fine motor		
DHCA: 0 vs 1-24 min	−0.07 (−0.66, 0.52)	−0.06 (−0.59, 0.47)
DHCA: 0 vs ≥25 min	−0.59 (−1.20, 0.02)	−0.66 (−1.21, −0.11)
Age	−0.03 (−0.04, −0.02)	−0.03 (−0.042, −0.018)

Data given as regression coefficients (95% confidence limits).

with 25 minutes or more of DHCA were aged 63 ± 16 years (40% women); there were 1 death and no strokes in this group.

The mean standardized testing results (Z-scores) are presented in Table I. These data are organized according to patient group (no DHCA; 1-24 minutes of DHCA; ≥25 minutes of DHCA), neuropsychologic domain (attention, processing speed, memory, executive function, fine motor function), and testing interval (PRE, EARLY, and LATE). Table I also includes the changes in mean Z-scores relative to baseline.

The analysis of covariance is presented in Table II. Relative to the group with no DHCA, fine motor and memory dysfunction occurred after the operation in the group with DHCA of 25 minutes or more, and age was a significant covariate. The interval between the operation and testing date for the EARLY and LATE evaluations was not a statistically significant predictor of performance in the analysis of covariance, despite the wide variability in the range in these intervals.

The multivariate logistic regression results for each domain are presented in Table III. DHCA of 25 minutes or more and advanced age were significant predictors of poor performance at the LATE evaluation for the memory and fine motor function domains. For all domains, negative neuropsychologic outcome (poor performance or inability to be tested) at the EARLY evaluation was a significant predictor of poor performance at the LATE evaluation (overall odds ratio, 5.27; $P < .01$). In the group with DHCA of less than 25 minutes, there were no significant decreases in neuropsychologic outcome (LATE) in any domain, compared with patients in the group with no DHCA. Because of the wide ranges in the intervals between the operation and testing, we also examined the effect of reclassifying all EARLY data collected (on inpatients) more than 14 days after the operation as "too ill to be tested" and excluding all LATE data collected (on outpatients) before 21 days after the operation. We found that this did not affect the magnitude or direction of the results shown in the multivariate analysis.

The probability of hospital discharge in each of the 3 patient groups is displayed graphically in Fig 1. DHCA of 25 minutes or more (odds ratio, 4.0; $P = .02$) was a determinant of prolonged hospital stay (>21 days). DHCA of 1 to 24 minutes was not a predictor of prolonged hospital stay, compared with cardiac surgical patients having no DHCA.

Discussion

The results of the current study indicate that DHCA and advanced age in adult patients undergoing thoracic aortic operations are associated with prolonged postoperative impairment in memory and fine motor function. Additionally, prolonged DHCA was associated with prolonged hospital stay.

It is possible that the impairment in memory function in patients with prolonged DHCA is related to injury to

Table III. *Probability of decline in late neuropsychologic outcome*

	Odds ratio	*P value*	*95% Confidence interval*
Attention			
DHCA: 0 vs 1-24 min	1.47	.507	0.47-4.58
DHCA: 0 vs ≥25 min	2.34	.126	0.79-6.96
Age	0.87	.115	0.74-1.03
EARLY outcome	8.78	.002	2.18-35.37
Processing Speed			
DHCA: 0 vs 1-24 min	1.09	.881	0.36-3.34
DHCA: 0 vs ≥25 min	1.38	.547	0.48-3.96
Age	1.13	.176	0.95-1.35
EARLY outcome	3.18	.012	1.29-7.80
Memory			
DHCA: 0 vs 1-24 min	1.38	.596	0.42-4.62
DHCA: 0 vs ≥25 min	3.47	.032	1.11-10.86
Age	1.21	.048	1.00-1.46
EARLY outcome	4.64	.003	1.69-12.75
Executive			
DHCA: 0 vs 1-24 min	0.93	.896	0.30-2.86
DHCA: 0 vs ≥25 min	0.91	.863	0.31-2.69
Age	0.98	.849	0.83-1.16
EARLY outcome	7.96	<.001	2.62-24.2
Fine motor			
DHCA: 0 vs 1-24 min	5.84	.013	1.44-23.62
DHCA: 0 vs ≥25 min	11.11	<.001	2.93-42.09
Age	1.36	.008	1.08-1.70
EARLY outcome	4.77	.005	1.59-14.36

the hippocampus. This region of the brain is the locus for the acquisition of new information and is particularly sensitive to anoxic or ischemic injury because of its high metabolic rate.[10] The independent risk for motor and memory dysfunction in older patients may be related to slower recovery because of a reduced brain reserve capacity.[11]

Both experimental[12] and clinical[13] studies support the idea that the duration of cooling and the temperature during DHCA are important determinants of the adequacy of cerebral protection and the duration of the arrest interval. Differences in these aspects of implementation of DHCA may account for some of the variability in outcome reported in earlier studies, some of which were carried out after very short intervals of cooling, especially in infants, and at higher core temperatures than reported here. Assuring that jugular venous blood is fully saturated is one way of monitoring the adequacy of cerebral metabolic suppression (and therefore cerebral cooling) before the institution of DHCA.

The only previous study (to the authors' knowledge) investigating neuropsychologic outcome after DHCA in adult patients was performed by Welz and associates.[6] In that study, 23 patients who had undergone DHCA were assessed in the late postoperative period (mean, 17 months after the operation; range, 8-40 months). The battery consisted of a computer test of tonic alertness and sustained attention, the Trail Making Test, digit span, and a verbal learning test. The patients' results were compared with those of 10 healthy subjects. The patient group performed more poorly than the reference group on all measures. The level of impairment in sustained attention correlated with duration of DHCA.

The clinical studies on the neurologic sequelae of DHCA in adults are limited and controversial with regard to the relationship between the length of DHCA and neurologic outcome. Svensson and associates[8] reviewed stroke and mortality rates in 656 adult patients undergoing DHCA. The length of circulatory arrest was a univariate, but not a multivariate, predictor of stroke. The multivariate predictors of stroke were history of cerebrovascular disease, previous aortic operation distal to the subclavian artery, and CPB time. The multivariate predictors of death were advanced age, Marfan's syndrome, concurrent distal aortic aneurysm, previous ascending aortic operation, CPB time, cardiac and renal complications, stroke, and DHCA times of 65 minutes or more.

Grabenwoeger and associates[14] retrospectively reviewed the results of 105 patients undergoing DHCA procedures. Age was a significant multivariate predictor of death and neurologic outcome, but DHCA time was not associated with an increased rate of adverse sequelae.

Our early experience indicated that there are 2 distinct types of neurologic outcome after DHCA in a thoracic aorta operation. Permanent neurologic sequelae observed in 7% of the patients were related to embolic strokes, with corresponding defects verified by computed tomography of the brain. The multivariate predictors of stroke were age, severe atheromatous involvement of the aorta, and descending aorta operation. The stroke incidence was not related to the duration of the arrest period and therefore was independent of the method of cerebral protection. Additionally, we found that 19% of patients had temporary neurologic dysfunction defined by clinical assessment as postoperative confusion, agitation, delirium, prolonged obtundation, or parkinsonism without localizing neurologic signs. The predictors of temporary neurologic dysfunction were duration of DHCA and patient age.[7] We believe that this clinical syndrome is a manifestation of subtle brain injury as the result of inadequate cerebral protection. It is quite likely that this syndrome corre-

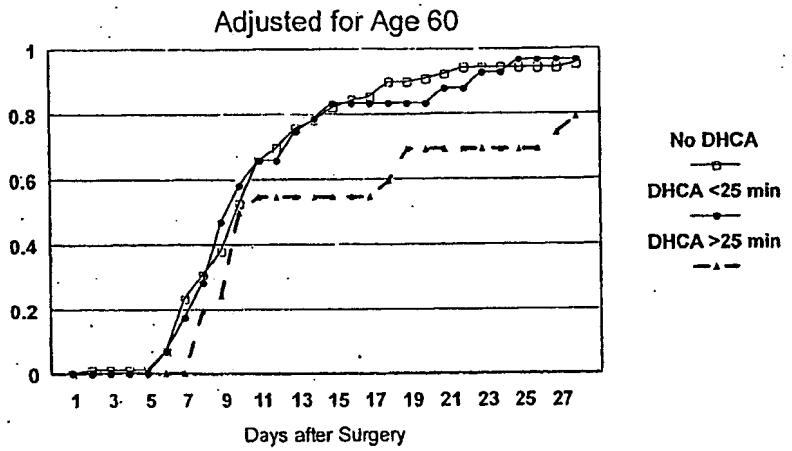

Fig 1. The probability of discharge from the hospital is plotted against the days after the operation for the 3 patient groups.

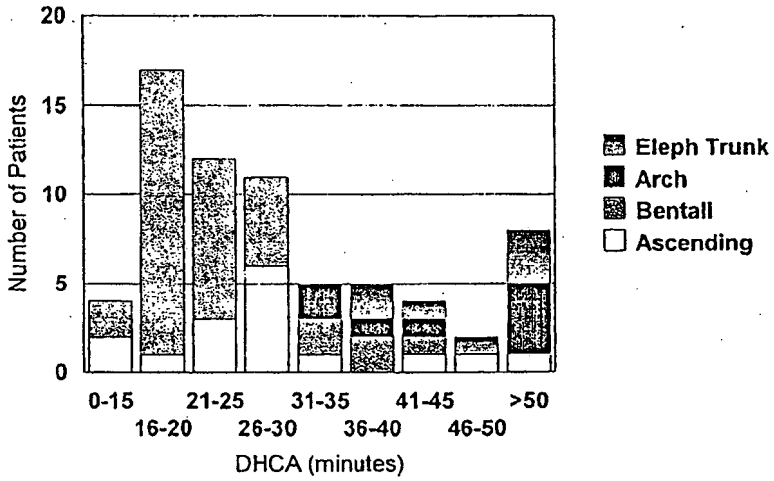

Fig 2. Distribution of surgical procedures according to duration of deep hypothermic circulatory arrest. *Eleph Trunk*, Elephant trunk procedure; *Arch*, aortic arch repair; *Bentall*, Bentall procedure; *Ascending*, ascending aortic repair.

lates with the neuropsychologic deficits currently reported. An investigation of this relationship in a larger cohort of patients is in progress.

The literature on children undergoing repair of congenital heart lesions is also controversial with regard to the relationship between DHCA duration and cerebral sequelae. Bellinger and associates[1] compared 171 patients randomized to DHCA or low-flow CPB for arterial switch procedures. One year after the operation, the group with DHCA had a lower mean Bayley Psychomotor Development Index, and a higher proportion of the group had scores of 2 standard deviations or more below the norm. The psychomotor development index score was inversely related to the duration of DHCA. The risk of neurologic abnormalities also increased with the duration of DHCA. Deficits were most prevalent in patients with DHCA lasting more than 45 minutes.[15]

Oates and associates[3] studied 114 children who had undergone DHCA (9-10 years previously) using intelligence and neuropsychologic tests and compared them to a group with CPB. Overall, there were no important differences between the 2 groups in neuropsychologic outcome. There was, however, a significant decrease in intelligence quotient scores with increasing DHCA time.

Wright and associates[5] assessed 32 children who had undergone a ventricular septal defect operation with DHCA (n = 17 children) versus CPB (n = 15 children). They found a higher incidence of developmental abnormality in the group with DHCA 7 to 72 months after

the operation. There are also a number of studies finding no influence of DHCA on cerebral outcome.[16-19]

The generalizability of the findings of the current study is limited by the exclusion of patients undergoing emergency operations and patients who were disoriented or excessively sedated before an operation. In addition, certain patients were lost to follow-up because they did not return for postoperative physician visits. The potential effect of these exclusions is uncertain, but because the cohort studied tended to be healthier patients (elective operation), it is possible that our results reflect a more optimistic assessment of neuropsychologic outcome.

We were concerned that dichotomizing neuropsychologic outcome could be a confounding factor because of the inherent difficulty in selecting appropriate cutoff values. However, the magnitude and direction of the multivariate results did not differ from the analysis of covariance, in which all of the cognitive domain outcomes are treated as continuous data (mean Z-scores). Moreover, in the continuous analyses, we lose informative data regarding the patients who could not perform tests because they were too ill or too impaired. In contrast, the analysis of dichotomous outcomes incorporates this information. These analyses are therefore complementary.

Another possible confounding factor is the subdivision of the patients with circulatory arrest, according to the duration of the arrest. The patients in the shorter arrest group were undergoing procedures such as ascending aortic replacement, whereas those in the longer arrest group were undergoing procedures such as aortic arch replacement. The distribution of the surgical procedures according to the length of DHCA is presented in Fig 2. The duration of the arrest in this clinical scenario is not necessarily an independent observation, but it is also a marker for a more complex operation and/or more severe atherosclerosis. In this study, therefore, it is impossible to separate the effects of the duration of circulatory arrest from the complexity of the procedures.

In summary, hypothermic circulatory arrest of 25 minutes or more and advanced age were associated with neuropsychologic impairment in fine motor and memory functions and prolonged hospital stay. The neuropsychologic outcome and length of hospital stay of patients undergoing periods of hypothermic circulatory arrest of less than 25 minutes were indistinguishable from patients undergoing cardiac operation without circulatory arrest. It remains to be seen whether modifications in technique, such as selective cerebral perfusion, retrograde cerebral perfusion, and new pharmacologic agents, may ameliorate the neuropsychologic deficits arising from DHCA.

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Discussion

Dr Richard A. Jonas (*Boston, Mass*). I appreciated Dr Reich sending me a copy of the manuscript. Simply by looking at the title page, I knew that this paper would make an important contribution. This was not just because this paper comes from Dr Griepp's group, which has made so many important contributions in the past to our understanding of DHCA. What was just as important to me was that the paper is a collaborative effort of several departments including neurology. The only important absence that I noted from the authorship or the acknowledgment section was a statistical consultant. Obviously, the statistical analysis of a study such as this is highly complex. As both a reader and associate editor of *The Journal of Thoracic and Cardiovascular Surgery*, I am greatly reassured when a statistician clearly places his or her name on a complex analysis such as this study involves.

One of the great advantages that my group has had in undertaking psychometric studies of patients after a cardiac operation is that we work with young children who undergo a uniform procedure for a uniform anomaly at a uniform age. Furthermore, it has been possible to persuade parents to return with the children at an extremely high rate of follow-up, so that in our own National Institutes of Health–supported study of circulatory arrest we had a 99% follow-up rate. The authors of this study, however, are in the difficult position that there is a wide range of complexity and severity of patients within their population and a higher incidence of more complex aortic arch operation in patients undergoing a longer duration of hypothermic circulatory arrest. Thus, as you have acknowledged, an equally valid explanation regarding the significant decline in psychometric testing after an operation might be the need for an arch operation versus an ascending aortic operation. This would seem to be quite plausible in view of the increased risk of atheromatous microembolism with an arch operation versus an ascending aortic operation. Do you believe that in the future there is any possibility that you will be able to randomize your patients in a more uniform population between shorter and longer durations of hypothermic circulatory arrest?

As an extension of that, you have chosen to dichotomize your analysis of duration circulatory arrest into 2 groups, a group with a duration less than 25 minutes and a group with duration longer than 25 minutes. You have explained that this was related both to being the median cutoff point and there being more patients with more complex conditions in the longer duration group. Perhaps in a sense this really supports the alternative explanation. Can you give us some rationale why you might have dichotomized into those 2 groups if you believed that in fact circulatory arrest duration was the explanation as to the differences rather than the difference in complexity? Did you attempt to analyze the duration of hypothermic circulatory arrest as a continuous variable? If so, what results did you obtain?

Many previous studies of circulatory arrest by surgical groups seem to be based on the premise that if the patient survives the operation, is not comatose, and does not have a dense hemiplegia or aphasia, it is likely he or she has not had any neurologic insult. This study demonstrates that hypothermic circulatory arrest may well be associated with subtle but important neuropsychometric deficits in adults.

Dr Reich. Regarding the future, I do not believe that it will be truly possible to randomize patients to longer arrests if they have relatively simple lesions, just for ethical purposes obviously, but I think that there is a likelihood that we may be able to do things such as selective cerebral perfusion or retrograde perfusion in a more scientific fashion in these patients. These techniques are being used selectively at the present time. I believe that is where you will probably see this sort of work, at least in the adult population.

Regarding the decision to split the patients with hypothermic arrest into the 2 groups, I will answer the second half of that question first. When we look at hypothermic circulatory arrest as a continuous variable, there is a difference in that the longer the arrest period the more the decrement in function. That was how we performed our analysis initially with an analysis of covariance. However, at the urging of my collaborators, specifically Drs Ergin and Griepp, we did split this patient population because we believe that there really is a rather dramatic difference between the patients who are in the shorter duration group and the longer duration group. I fully acknowledge in this article, and perhaps even in the future, that we will probably never be able to fully separate out the effects of the shorter procedures, which are obviously more simple, from those that are more complex.

Let me finally reassure you that Dr Sliwinski, who is one of our coauthors, is indeed a biostatistician whose appointment is in the Department of Neurology at Albert Einstein. Rest assured that we were rigorously supervised by our biostatistician.